

REMARKS

Claims 1-12 and 15-18 are rejected and claims 13-14 have been objected to. Applicants herein amend claims 1-5 and 11-14; cancel claims 15-18; and add new claims 19-23. Claims 1-14 and 19-23 are currently pending.

Claim 1 is amended to recite "wherein said dUTP replaces from about 10 to about 50% of said dTTP in said reaction mixture". Support for this amendment can be found, for example, in original claim 3 and at paragraph 0073 of the published application. Claim 1 is amended also to recite "at least one primer, wherein said primer has at least one uracil base incorporated therein". Support for this amendment can be found, for example, in original claim 5 and also at paragraphs 0043 and 0046. Accordingly, the amendments to claim 1 add no new matter.

There is also no issue of new matter with respect to the dependent claims. Claims 2 and 3 are amended to recite that dUTP replaces dTTP "from about 10 to about 30%" and "from about 20 to about 40%", respectively. Support for these ranges occurs in the original specification, for example, at paragraphs 0073 and 0066, respectively. Claim 4 is amended merely to correct an apparent typographical error where the word "of" was omitted. Claim 5 is amended to recite "wherein said reaction mixture comprises a primer pair," providing antecedent basis for "the primer pair" referred to in that claim. The amendment finds support in the original specification, for example, at original claim 15. Finally, claim 13 is amended to remove dependencies to multiple prior claims, while claims 11 and 12 are amended to recite "wherein said nucleic acid is DNA". There is also no issue of new matter with respect to this amendment, for example, as paragraph 0029 specifically defines "nucleic acid" as referring to both DNA and RNA.

There is also no issue of new matter with respect to new claims 19-21. Paragraph 0070, for example, provides support for using sorbitol or mannitol, as well as support for the specific ranges claimed.

With respect to the amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments, for example, in future continuation and/or divisional applications.

Corrected Drawings

The Examiner requested new corrected drawings, because some of the Figures allegedly were not legible. Action at page 2. Applicants submit herewith new corrected drawings in compliance with 37 CFR 1.121(d). Applicants respectfully note that the contents of the new Figures are all readily legible.

Claim Objections

The Examiner objected to claims 13 and 14 for containing improper multiple dependencies. Action at page 2. Claims 13 and 14 depend from claims 11 and 12, which in turn originally depended from claims 1-10. Applicants have amended claim 13 to depend solely from claim 11, thus obviating the objection. Applicants accordingly request withdrawal of these objections.

The Examiner also objected to claim 14 for apparently omitting the word "of" in the phrase "further comprising at least one additional unconventional nucleotide, wherein the combined concentration said dUTP" Action at page 2. Applicants respectfully note that this phrase occurs in claim 4 rather than claim 14, and have amended claim 4 to include the missing word. Accordingly, Applicants respectfully request withdrawal of this objection as well.

Rejections Under 35 U.S.C. § 112, 2nd Paragraph

Claims 5 and 6 are rejected under 35 U.S.C. § 112, 2nd paragraph, as allegedly being indefinite. Action at page 3. Specifically, the Examiner purports that antecedent basis is lacking for "the primer pair," which is recited in claim 5. *Id.*

As noted above, claim 5 has been amended to recite "wherein said reaction mixture comprises a primer pair," thereby providing antecedent basis and removing any ambiguity from the claims. Accordingly, Applicants earnestly and respectfully request withdrawal of the indefiniteness rejections.

Rejections Under 35 U.S.C. § 112, 1st Paragraph

Claims 11 and 12 are rejected under 35 U.S.C. § 112, 1st paragraph, as allegedly not being enabled. Action at pages 3-4. Specifically, the Examiner states that "the specification, while being enabling for a method for reducing primer aggregation during an amplification [of] a target nucleic acid, *wherein said target*

nucleic acid is DNA, does not reasonably provide enablement for the method, wherein said target nucleic acid is RNA.” *Id* (emphasis added). The Examiner points to the fact that ATP, TTP, CTP and dCTP are recited as being “conventional” nucleotides, such that dUTP is considered unconventional. Action at page 4.

Without acquiescing in any way to the Examiner’s contentions, claims 11 and 12 have been amended, as noted above, to specify that “~~said nucleic acid is DNA.~~” This amendment reflects the Examiner’s acknowledgement that the specification is indeed enabling for the methods of claims 11 and 12 where the target nucleic acid is DNA. Action at page 4.

Accordingly, Applicants respectfully submit that the claims as currently amended present no enablement issues, and thus respectfully request reconsideration and withdrawal of the 112, 1st paragraph, rejections.

Rejections Under 35 U.S.C. § 102

The Fraiser Rejections

Claims 1-4 and 7-12 are rejected under 35 U.S.C. § 102(b) as being anticipated by Fraiser *et al.*, US Patent No. 5,536,649 (hereinafter “Fraiser”). Action at pages 5-6. Specifically, the Office alleges that Fraiser provides a reaction mixture comprising dNTPs and dUTP, and construes certain dUTP and dTTP concentration ranges disclosed in Fraiser as providing 50% replacement of dTTP by dUTP. *Id*. Applicants respectfully traverse as Fraiser, accurately construed, fails to teach a reaction mixture where dUTP replaces from about 10% to about 50% of dTTP, as currently recited in amended claim 1. Nor does Fraiser teach a reaction mixture containing at least one primer having at least one uracil base incorporated therein, again as now required by amended claim 1.

Applicants respectfully traverse the assertion that Fraiser discloses concentration ranges representing 50% replacement of dTTP with dUTP in a reaction mixture. The Office relied on Fraiser’s disclosure of a dUTP concentration of “about 0.5-4 mM” and a concentration of “about 0.1-1 mM of each dNTP other than dUTP.” Column 5, lines 50-52. Applicants respectfully note, however, that the Office arrived at the 50% number by improperly selecting and comparing the low end of the dUTP concentration range with the high end of the dTTP concentration range, even though such a selection is inconsistent with all of the more specific teachings in Fraiser regarding appropriate ranges.

Fraiser teaches methods for decontamination after strand displacement amplifications, by using dUTP in the amplification reactions and then destroying contaminating amplicons from prior reactions (which will necessarily contain Uracil) before subsequent reactions are carried out. Notably, Fraiser repeatedly emphasizes the importance of using excess dUTP to effectuate this approach. Fraiser teaches that "[m]ost preferably, dUTP *fully* replaces TTP in the amplification reaction and is included *at a higher concentration* than each of the other three nucleotides to drive the reaction for *maximum substitution*." Column 5, lines 12-15 (emphases added). Further, after providing the concentration ranges relied on by the Office, the specification admonishes that "[u]sing the guidelines provided above only routine optimization is required to determine the appropriate relative concentrations of dUTP, ... to produce *full* dU-substitution of the amplification product." Column 6, lines 20-24 (emphasis added). Accordingly, Fraiser explicitly instructs one to select a dUTP/dTTP relative concentration that favors maximum substitution with dUTP. Selecting to use the lowest end of the dUTP concentration range with the uppermost end of the dTTP concentration range would be entirely inconsistent with these more specific teachings.

Indeed, Fraiser's specific examples as well as their claimed embodiments further underscore the importance of using excess dUTP to achieve maximum substitution. Examples 1 and 2 both use 0.5 mM dUTP and 0.2 mM of each dATP, dCTP and dGTP. Notably, and unlike the presently-claimed invention, no dTTP is used in either of the Fraiser examples, thereby ensuring 100% substitution of dTTP by dUTP. Further, the dUTP is used at two and a half times the concentration of any of the other three dNTPs, again exemplifying the requirement for excess dUTP. The claimed embodiments recited in independent claims 1, 9, 12 and 13 further emphasize the importance of 100% substitution and the use of excess dUTP. As with the worked Examples, all of the claims omit dTTP from the claimed reaction mixtures.

In light of the disclosure as a whole, Applicants respectfully submit that selecting to compare the lowest concentration of the dUTP range with the highest concentration of the dTTP range is inconsistent with Fraiser's teachings. Fraiser instructs one to select relative concentrations within the stated ranges to ensure *maximal* substitution of dTTP by dUTP, and the worked Examples and claimed embodiments all illustrate that this is achieved using an excess of dUTP relative to

all of the conventional nucleotides, and typically no dTTP whatsoever. In contrast, claim 1 as presently amended requires that dUTP replace only from about 10 to about 50% of dTTP in the reaction mixture. Failing to teach or even suggest this element the claim, Fraiser cannot anticipate claim 1 as currently amended.

In addition, Applicants have amended claim 1 to recite that the reaction mixture also comprises at least one primer having at least one uracil base incorporated therein, an element also absent in Fraiser. Indeed, the Examiner acknowledged that "Fraiser *et al.* do not explicitly teach that a primer should contain a uracil base therein" Action at page 7. Accordingly, Fraiser clearly fails to teach this claim element as well and thus cannot anticipate amended claim 1 for this additional reason.

Similarly, Fraiser cannot anticipate claims 2-4 nor 7-12, that each depend directly from amended claim 1. Furthermore, claim 12 explicitly excludes the use of "an enzyme degradation step employing UNG," whereas Fraiser obviously relies on such a step to effectuate its methods. Consider, for example, Fraiser's description that "amplicons from a prior SDA reaction performed with incorporation of dU can be rendered unamplifiable by UDG in a subsequent SDA reaction" Column 6, lines 33-35 (UNG being synonymous for UDG). Accordingly, the exclusion of a UNG step from claim 12 provides yet another point of novelty over Fraiser with respect to this claim.

For at least one or more of the above reasons, Applicants earnestly and respectfully request reconsideration and withdrawal of the 102(b) rejections based on Fraiser and directed at claims 1-4 and 7-12.

The Monforte Rejections

Claims 15 and 16 are rejected under 35 U.S.C. § 102(b) as being anticipated by Monforte *et al.*, US Patent No. 5,830,655 (hereinafter "Monforte"). Action at page 6. Specifically, the Examiner alleges that Monforte provides a mixture comprising a primer pair comprising at least one uracil therein. *Id.*

As noted above, Applicants have cancelled claims 15-18, rendering moot the Monforte rejections directed at these claims.

Rejections Under 35 U.S.C. § 103

Claims 5-6 and 15-18 are rejected under 35 U.S.C. § 103(a) as being obvious in view of Fraiser and further in view of Haberhausen *et al.* US 6,248,522 (hereinafter "Haberhausen"). Action at pages 6-8. Specifically, the Office alleges that it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Fraiser with the U-containing primers taught by Haberhausen to arrive at the claimed invention. Action at pages 7-8. Applicants respectively note that the rejections directed at claims 15-18 are rendered moot as these claims have been cancelled.

With respect to claims 5 and 6, Applicants respectfully traverse because Fraiser fails to disclose at least two elements of amended claim 1, and hence of claims 5 and 6 that depend therefrom, and Haberhausen fails to remedy either of these deficiencies. As detailed above, Fraiser fails to teach or suggest a reaction mixture where dUTP replaces from about 10% to about 50% of dTTP, as required by the amended claims. Conversely, Fraiser teaches using relative concentrations of dUTP and dTTP to achieve maximal substitution, requiring an excess of dUTP.

Haberhausen does nothing to refute this teaching in Fraiser, and in fact further confirms that excess dUTP should be used. Haberhausen is directed to simplifying approaches for reducing cross-contamination by preventing the reactivation of degradation enzymes, such as UDG. See column 2, lines 51-54. As was the case in Fraiser, all of Haberhausen's examples use no dTTP and several fold excess of dUTP over any of the other three nucleotides. In particular, Examples 1 and 3 both use 200 μ M each of dATP, dCTP and dGTP and 600 μ M dUTP, representing 100% replacement of dTTP by dUTP in the reaction mixtures, as well as a three fold excess of dUTP compared to the other nucleotides. These examples further confirm the error of interpreting Fraiser's disclosure as teaching other than the use of excess dUTP compared to dTTP.

A *prima facie* case for obviousness requires that the cited references teach every limitation of the claimed invention, but neither Fraiser nor Haberhausen teach or suggest a reaction mixture where dUTP replaces only from about 10% to about 50% of dTTP, as required by the amended claims. Accordingly, Applicants respectfully submit that the claims as currently amended are not obvious in view of the cited art.

In addition, there is no *prima facie* case for obviousness with respect to Fraiser's second missing element. As the Examiner acknowledges, Fraiser fails to teach a reaction mixture comprising at least one primer having at least one uracil base incorporated therein (Action at page 7), an element now required by the amended claims. As noted above, the Office then alleges that Haberhausen provides this missing element. Applicants respectfully submit, however, that there is no motivation to combine the U-containing primers of Haberhausen with the teachings of Fraiser because Haberhausen teaches the use of U-containing primers only as a separate and alternate approach.

According to the Office, Haberhausen discloses "a mixture comprising dNTPs, dUTP and primers comprising one or more uracil bases therein, in a method of amplifying a target nucleic acid" (emphasis added), and specifically refers to column 3, line 42 of the specification. Action at page 7. Applicants respectfully note, however, that the sentence referred to only teaches using dUTP or a U-containing primer, but not both together: "For this dUTP *or* a U-containing primer is used in the amplification reaction instead of or in addition to the normal dTTP ..." (emphasis added). As Haberhausen clearly and explicitly refers to using only dUTP or U-containing primers in the alternative, Haberhausen provides no motivation to combine these separate approaches or to combine the U-containing primers with Fraiser's teachings.

Haberhausen further underscores the point that only one of the two options are to be used at column 1, lines 35-51. Here, the specification explicitly describes the approach of using mononucleotides not naturally present in nucleic acid, and the approach of using primers containing uracil, as two separate and alternate approaches. Indeed, the specification states "An *alternative* method utilizes primer containing uracil *instead of* mononucleotides containing uracil." Column 1, lines 47-48 (emphases added). Rather than providing any motivation to combine the approaches, Haberhausen expressly dictates their separate use, where one approach would only be used instead of or as an alternative to the other. Without any motivation to combine the two approaches, Haberhausen cannot remedy Fraiser's acknowledged lack of U-containing primers and thus no *prima facie* case for obviousness can be made.

For at least one or both of the above reasons, Applicants respectfully submit that there is no *prima facie* case for obviousness based on the cited references, and

earnestly and respectfully request reconsideration and withdrawal of the 103(a) rejections.

CONCLUSION

Applicants respectfully submit that all claims under active examination are neither anticipated nor rendered obvious in view of the art references cited against this application. Applicants thus earnestly and respectfully request timely allowance of pending claims 1-14 and 19-23.

If a telephone call would help expedite any aspect of the prosecution of the instant application, Applicants encourage the Examiner to contact the undersigned by telephone at (415) 318-1200 or by fax at (415) 318-1300.

Respectfully submitted,
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